Episodic vestibular syndrome - Vestibular migraine vs. Menière's disease

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EAN Spring School 2018
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Transitory / episodic vertigo

Most frequent central causes
- Vestibular migraine
- Vertebrobasilar TIA
- Episodic ataxia type 2 (EA 2)
- Epileptogenic vertigo
- Central paroxysmal positional vertigo (CPPV)

Most frequent peripheral causes
- Menière's disease
- Benign paroxysmal positional vertigo (BPPV)
- "Mild" vestibular neuritis
- Vestibular paroxysmia

New developments

Vestibular migraine (VM)
- Now listed as a diagnosis (A1.6.6) in the appendix of the International Classification of the Headache Society (ICHD III).

Menière's disease (MD)
- New diagnostic criteria according the Classification Committee of the Bárány Society (2015)

Overlap-syndrome

Overlap between vestibular migraine and Menière's disease
- Increased prevalence of migraine in patients with Menière's disease.
- Fluctuating hearing loss, tinnitus and aural fullness also seen in VM, but hearing loss more subtle than with Menière's disease.
- Caloric irrigation triggered migraine attacks within 24h in up to 49% of predisposed patients.
- 13% of patients meet diagnostic criteria for both VM and Menière's disease.
- Menière's disease as atypical variant of migraine?
Clinical presentation of VM and MD – theory and real life situation

- Updated diagnostic criteria
- Clearly overlapping clinical presentation at the bedside

→ How to interpret these findings?
→ Which clinical and additional findings help in differentiating VM from MD?

Vestibular migraine - update

- Second most frequent cause for episodic vertigo/dizziness after the benign paroxysmal positional vertigo.
- Most frequent cause for an episodic, non-triggered vertigo/dizziness.
- Lifetime prevalence about 1%
- Women are affected 5x more often.
- Vertigo attacks often delayed by years or decades after onset migraine headaches. Accumulated at the onset of the menopause, while migraine headaches at the same time become less frequent.

Vertigo + migraine = vestibular migraine?

- Dizziness/vertigo in up to 50% of all migraine headache attacks
- Occurrence of dizziness/vertigo and migraine may be coincidence (Prevalence of migraine = 10-25%, prevalence of vertigo = 5-10%).
- In a case series of newly diagnosed migraine patients 10% met the diagnostic criteria for vestibular migraine (Cho et al. 2015).

Vestibular migraine - key facts

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- Most frequent cause for an episodic, non-triggered vertigo/dizziness.
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Vestibular migraine - diagnostic criteria (ICHD 3)

A. 25 episodes fulfilling criteria C and D
B. A current or past history of migraine (with / without aura) according the diagnostic criteria of the International Headache Society (IHS)
C. Vestibular symptoms of moderate or severe intensity, lasting between 5min and 72h.
D. At least 1 of those 3 migraine-associated symptoms in at least 50% of the episodes
   1. Headache with at least 2 of the following 4 characteristics
      i. Unilateral location
      ii. Pulsating quality
      iii. Moderate or severe intensity
      iv. Aggravation by routine physical activity
   2. Photophobia and phonophobia
   3. Visual aura
E. No better accounted four by another ICHD-3 diagnosis or by another vestibular disorder.

Pathophysiology of vestibular migraine – vestibulo-thalamo-cortical pathways

Reciprocal communications between brainstem vestibular nuclei and the structures that modulate trigeminal nociceptive inputs → trigemino-vestibulocochlear reflex

Headache classification committee of the IHS. Cephalalgia 2018; 38(1): 1–211

Neuhauser et al. (2006). Neurology; 67:1028–33
fMRI in vestibular migraine

Clinical presentation: dizziness and central positional nystagmus for 72 hours


Increased thalamic activation to caloric irrigation in VM

The magnitude of thalamic activation was positively correlated with the frequency of migraine attacks in patients with VM

Russo et al. Neurology 2014;82:1–7

Vestibular migraine: clinical presentation

Strongly varying semiology:
- Rotational vertigo
- Increased motion sensitivity for head movements
- Position-dependent dizziness
- Intolerance of visual stimuli

Duration varies broadly:
- 20% between 5 and 60 minutes
- But symptoms may last only seconds or may be chronic.

Variable association between vertigo and headache:
- Present at the same time in only 70% of cases.

Ictal ocular motor and vestibular symptoms in VM

Pathologic nystagmus in 70% (spontaneous nystagmus or positional nystagmus)
- Gait ataxia in 95%
- Central vestibular dysfunction in 50%, peripheral vestibular dysfunction in 15%.

Interictal ocular motor and vestibular signs in VM


Stolte et al. 2014 Cephalalgia


Vestibular testing

- Horizontal video-head-impulse test (37 vs. 9%, p=0.025) and caloric irrigation (67 vs. 22%, p=0.002) were significantly more often abnormal in Menière’s disease than in vestibular migraine.¹
- Horizontal video-head-impulse test abnormal in 8% of all vestibular migraine patients.²

² Yoo et al. Clin Otolaryngol. 2015
² Chu et al. The Journal of Headache and Pain 2015
³ Staab Continuum 2012;18(5):1118-1141

Vestibular migraine - associated disorders

- Associated disorders:
  - Menière’s disease
  - BPPV
  - Motion sickness
  - chronic subjective dizziness
- 57% with associated disorders that also trigger vestibular symptoms.¹
- Migraine: 2-times increased risk, to develop a benign paroxysmal postional vertigo.²
- Anxiety disorders and depression in 20-35%.³

² Chu et al. The Journal of Headache and Pain 2015
³ Staab Continuum 2012;18(5):1118-1141

Treating vestibular migraine – current evidence

Vestibular migraine: treatment

In analogy to the treatment of migraine headaches

Acutely during the attacks:

| NSAR (e.g. Naproxen 500mg or Ibuprofen 400-800mg) |
| Aspirin 500-1000mg |
| Paracetamol 1000mg |
| Combined analgetics |
| Triptans |
| • oral (e.g. Sumatriptan 25-50mg, Naratriptan 2.5mg, Zolmitriptan 2.5-5mg) |
| • nasal (Zolmitriptan 2.5-5mg, Sumatriptan 20mg) |
| • s.c. (Sumatriptan 6mg) |
| Ergotamine derivatives |

→ only retrospective studies!
Pharmacological agents for the prevention of vestibular migraine (Review)

Maldonado Fernández M, Briel J, Irving G, Murcia L, Kivkis J, Stepp M

We identified one ongoing study comparing metoprolol to placebo. “... we found no evidence from RCTs to answer the question set out in the review objectives.”

Conclusions

- Study quality overall weak to moderate: prospective, randomised controlled studies rare.
- No placebo-controlled studies!
- Overall most convincing support for venlafaxine:
  - Efficacy in two prospective, randomised studies1,2
  - Broader treatment spectrum than sodium valproate, flunarizine3 and propranolol1.
- Optimal dosage unclear: 37.5mg/d sufficient?
- Data less convincing for cinnarizine + dimenhydrinate and acetazolamide (selection bias1) and more side-effects (acetazolamide).

Life style modifications

- Relaxation exercises
- Mild endurance training (2-3x 45min per week), Attention: no RCTs3 Physical activity may also trigger headaches.
- Sleep hygiene (regular sleep-wake-cycles)
- Behavioral treatment, Thai-Chi, autogenic training2,3
- Acupuncture1,5

Migraine prophylaxis – the Zurich approach

For mild or moderate symptoms
  - Magnesium (Initial 5mmol/d, increase by 5mmol/d every 7 days, target dose 30mmol/D) PLUS
  - Riboflavin (Vitamin B2, 400mg/d)
  - Duration of combined treatment: at least 8-10 weeks

For severe symptoms
  - Venlafaxin (Efferon), initially 37.5mg/d, target dose 150mg/d for cases with accompanying psychiatric disorders (depression, anxiety)
  - Topiramat (Topamax), voltage-gated sodium-channel blocker, initially 25mg/d, target dose 100mg/d. Attention: psychomotor slowing (10% of patients), weight loss, decreased potassium levels.
  - Flunarizin (Bibleml®), selective calcium-antagonist, initially 5mg at night, target dose 10mg) if vestibular symptoms dominate. Attention: weight gain, worsening of pre-existing depression or extrapyramidal tract signs.

*Vestibular migraine: prophylactic treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Side effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol 80-200mg/d (Level A)</td>
<td>Fatigue, hypotension, impotence, depression, bradycardia</td>
</tr>
<tr>
<td>Sodium valproate 300-1000mg/d (Level A)</td>
<td>Fatigue, hypotension, impotence, depression, bradycardia</td>
</tr>
<tr>
<td>Topiramate 200-300mg/d (Level A)</td>
<td>Cognitive impairment, weight loss</td>
</tr>
<tr>
<td>Flunarizine 1-2mg/kg/d (Level A)</td>
<td>Dryness, weight gain, tinnitus, neuroendocrine and other side effects</td>
</tr>
</tbody>
</table>

Venlafaxine: 25-75mg/d (Level B) Selective, anticholinergic side-effects, sedation black

Calcium channel blockers
  - Flunarizine 1-2mg/kg/d Drowsiness, weight gain, depression
  - Dihydralazine 250-750mg/d (Level B) Caudal hypertension, depression
  - Cinnarizine 30mg/d (Level A) Psychomotor slowing, dizziness, increased blood pressure, headache
  - Amlodipine 5-10mg/d (Level B) Rash, oedema, weight gain, depression

Anticonvulsants
  - Sodium valproate 300-1200mg/d (Level A) Evening anorexia, depression, anxiety, weight gain
  - Topiramate 200-300mg/d (Level A) Cognitive impairment, weight loss
  - Carbamazepine 200-300mg/d (Level B) Sedation, anticholinergic side-effects, sedation black

Non-pharmaceutical treatment

- Magnesium 30mmol/d Diarrhea
- Vitamin B2 (Riboflavin) 400mg/d
- Coenzym Q10 150mg/d Gastrointestinal complaints

Update 2018!

- Recently published studies:
  - Propranolol vs. venlafaxine (Efferon)1
  - Cinnarizine + dimenhydrinate (Arliesint)2
  - Venlafaxine (Efferon) vs. sodium valproate vs. flunarizine (sibelium)3
  - Acetazolamide (Diamox)4

2 Jafari et al. Headache (2011) 51:899-911
3 Liu et al. Neurol Sci. 2017;38:1171
4 Teggi et al. Eur Arch Otorhinolaryngol. 2020;277(11):2663-71
5 Laryngoscope. 2016;126(1):169-177
Menière’s disease

Diagnostic criteria according to the Classification Committee of the Bárány Society (2015)

**Definite Menière’s disease**
- A. Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours.
- B. Audiometrically documented low- to medium frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo.
- C. Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear.
- D. Not better accounted for by another vestibular diagnosis.

**Probable Menière’s disease**
- A. Two or more episodes of vertigo or dizziness, each lasting 20 minutes to 24 hours.
- B. Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear.
- C. Not better accounted for by another vestibular diagnosis.

Menière’s disease - diagnostics

<table>
<thead>
<tr>
<th>Low-frequency hearing loss</th>
<th>Transient loss of saccular function in the attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right acute - normal</td>
<td>Left acute – no response</td>
</tr>
<tr>
<td>Right after 48h - normal</td>
<td>Left after 48h - recovery</td>
</tr>
</tbody>
</table>


Single subject data – bilateral Menière’s disease

- **AB (%) 67% ( cutoff ≤ 30%)**
- **Reduced peak-to-peak amplitude (3.64 μV, 5th percentile = 5.8 μV)**
- **Bilaterally absent bcVEMPs**


Menière’s disease – acute peripheral vestibulopathy

Discrepancy between video-head-impulse test (vHIT) and caloric irrigation in MD

- **Normal labyrinth**
  - Warm side: No nystagmus, hydrostatic pressure elevates stimulated and cupula bent.
  - Cool side: Nystagmus, Hydrostatic pressure decreases and cupula bent.

- **Hypnic labyrinth**
  - Warm side: No Nystagmus, hydrostatic pressure decreases and cupula bent.
  - Cool side: Nystagmus, Hydrostatic pressure decreases and cupula bent.

### Vestibular migraine vs. Menière's disease

<table>
<thead>
<tr>
<th>Duration of attacks</th>
<th>Vestibular migraine</th>
<th>Menière's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>5min-72h</td>
<td>20min – 12h (24h)</td>
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<table>
<thead>
<tr>
<th>Type of dizziness</th>
<th>Vestibular migraine</th>
<th>Menière's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>Spontaneous</td>
<td></td>
</tr>
<tr>
<td>(rotational/non-</td>
<td>(rotational/non-</td>
<td></td>
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<tr>
<td>directional)</td>
<td>directional)</td>
<td></td>
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<table>
<thead>
<tr>
<th>Accompanying symptoms</th>
<th>Vestibular migraine</th>
<th>Menière's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>Headaches</td>
<td></td>
</tr>
<tr>
<td>Photo-/phonophobia</td>
<td>Photo-/phonophobia</td>
<td></td>
</tr>
<tr>
<td>Visual aura</td>
<td>Visual aura</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Dizziness types</th>
<th>Vestibular migraine</th>
<th>Menière's disease</th>
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<tbody>
<tr>
<td>Position-dependent</td>
<td>Position-dependent</td>
<td></td>
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<tr>
<td>Motion-induced</td>
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<tbody>
<tr>
<td>Migraine headaches</td>
<td>Migraine headaches</td>
<td></td>
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<tr>
<td>Headaches (IHS)</td>
<td>Headaches (IHS)</td>
<td></td>
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</tbody>
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| Position-dependent    | Migraine headaches  |
| Motion-induced        | Headaches (IHS)    |

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<thead>
<tr>
<th>Ocular motor findings</th>
<th>Vestibular migraine</th>
<th>Menière's disease</th>
</tr>
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<tbody>
<tr>
<td>Impaired VOR-suppression</td>
<td>Impaired VOR-suppression</td>
<td></td>
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<table>
<thead>
<tr>
<th>Vestibular test results</th>
<th>Vestibular migraine</th>
<th>Menière's disease</th>
</tr>
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<tbody>
<tr>
<td>Ictal: nystagmus (70%)</td>
<td>Ictal: nystagmus (70%)</td>
<td></td>
</tr>
<tr>
<td>Interictal: HIT abnormal (26%)</td>
<td>Interictal: HIT abnormal (26%)</td>
<td></td>
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<tr>
<th>Cochlear findings</th>
<th>Vestibular migraine</th>
<th>Menière's disease</th>
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<tr>
<td>Aural fullness, subjective hearing loss</td>
<td>Aural fullness, subjective hearing loss</td>
<td></td>
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<th>Imaging</th>
<th>Vestibular migraine</th>
<th>Menière's disease</th>
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<tr>
<td>Increased rate of white matter lesions</td>
<td>Endolymphatic hydrops</td>
<td></td>
</tr>
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### Clues to distinguish VM from MD

- **Hydrops MRI Gd intratympanal - findings**
  - Normal
  - Increase of the endolymphatic space → hypointense on MRI
  - Mild hydrops (grade I)
  - Severe hydrops (grade III)

- **Hydrops MRI Gadolinium intratympanal - findings**
  - Mild endolymphatic hydrops
  - Severe endolymphatic hydrops

- **Hydrops MRI Gadolinium i.v. → diffuses into perilymphatic space**

- **Hydrops MRI - sensitivity**

<table>
<thead>
<tr>
<th>Table 1. Level of evidence for treatment options in Menière's disease</th>
<th>Sharon et al. (2015). Curr Treat Options Neurol. 2015;17:14</th>
</tr>
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<tbody>
<tr>
<td>Type of treatment</td>
<td>Specific treatment</td>
</tr>
<tr>
<td>Delayed saturation</td>
<td>Salt restriction</td>
</tr>
<tr>
<td>Oral pharmacotherapy</td>
<td>Enhancers</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>2b</td>
</tr>
<tr>
<td>Vestibular rehabilitation</td>
<td>Vestibular rehabilitation</td>
</tr>
<tr>
<td>Surgical therapy</td>
<td>Vestibular rehabilitation</td>
</tr>
<tr>
<td>Other</td>
<td>Vestibular rehabilitation</td>
</tr>
</tbody>
</table>

**EH** = endolymphathische Hydrops; **MD** = Morbus Ménière

- **Evidence for different treatment options**

`:1`
Conclusions 1

- Vestibular migraine:
  - Vestibular migraine in 10% of all migraine patients
  - Trigemino-vestibulocochlear reflex as possible underlying pathomechanism
  - Broad spectrum of clinical presentation
  - Relevant overlap to Menière’s disease
  - Treatment: in analogy to migraine headaches

- Menière’s disease
  - Combination of vestibular and cochlear symptoms mandatory
  - Treatment: no good evidence that betahistine improves the outcome.

Conclusions 2

- "(...) confirms a considerable overlap of symptoms in MD, VM, and pVM. In particular, we could not identify any highly specific symptom for one of the three entities. It is rather the combination of symptoms that should guide diagnostic reasoning." (Lopez-Escamez et al. 2015)

- Pragmatic treatment approach \(\rightarrow\) treat the most probable cause first
- Promising new diagnostics: hydrops MRI
- Still important: pure tone audiogram obtained during the attack.